Radiation treatment in prostate cancer: balancing between tumor control and toxicity
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Chapter 7

Increased Risk of Biochemical and Clinical Failure for Prostate Patients with a Large Rectum at Radiotherapy Planning: Results from the Dutch Trial of 68 Gy versus 78 Gy

Wilma D Heemsbergen, Mischa S Hoogeman, Marnix G Witte, Stéphanie TH Peeters, Luca Incroci, Joos V Lebesque

ABSTRACT

**Purpose:** To investigate whether a large rectum filling visible on the planning CT scan was associated with a decrease in freedom from any failure (FFF) and freedom from clinical failure (FFCF) for prostate cancer patients.

**Patients and methods:** Patients from the Dutch trial (78 Gy vs. 68 Gy) with available acute toxicity data were analyzed (n = 549). A 10 mm margin was applied for the first 68 Gy, 0-5 mm for the 10 Gy boost. The dose in the seminal vesicles (SV) was prescribed within four treatment groups according to the estimated risk of SV involvement. Two potential risk factors (RFs) for a geometric miss were defined: anorectal volume ≥ 90 cm³ and at least 25 % of treatment time diarrhea (RF1), and the mean cross-sectional area (CSA) of the anorectum (RF2). We tested whether these were significant predictors for FFF and FFCF within each treatment group.

**Results:** Significant results were observed only for patients with a risk of SV involvement > 25 % (dose of 68-78 Gy to the SV, n = 349). We found a decrease in FFF (p = 0.001) and FFCF (p = 0.01) for the 87 patients with RF1 (for RF2: p = 0.02 and 0.01, respectively). The estimated decrease in the FFCF rate at 5 years was 15 %.

**Conclusions:** Tumor control was significantly decreased in patients with a risk of SV involvement > 25 % and at risk for geometric miss. Current image guidance techniques offer several solutions to geometrically optimize the treatment. Additional research is needed to evaluate whether geometric misses can be prevented using these techniques.

Introduction

In the past decades, conformal radiotherapy (RT) has become the standard treatment technique for prostate cancer. This “high dose - high precision” treatment requires accuracy within millimeters with regard to delineation of the target, patient setup, and organ motion, because the current clinically applied margins are in the range of 8 - 15 mm. [1-3]. This also implies that the anatomical patient model available from the planning CT scan should be representative for the situation during the treatment period. In 2005, Dearmaley et al. [1] published data from a pilot study in which they had randomized patients between a standard or high radiation dose and between
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a 1-cm or 1.5-cm margin. Their results showed no decrease in tumor control for the 1-cm margin compared with the 1.5-cm margin, implying that a 1 cm margin is "safe" during conformal radiotherapy. Recently, De Crevoisier et al. [4] published data in which they concluded that the applied margins (of 7.5-15 mm to the block edge for the boost) were not safe for patients with a distended rectum visible on the planning CT scan. They noticed a decrease of almost 30% in tumor control for the subgroup with a cross sectional area (CSA) of the rectum greater than the median value of 11 cm².

In a previous study of our own group, Hoogeman et al. [5] studied the rotational position of the prostate as a function of rectal volume. In their study, the data of 19 patients for whom a planning CT scan was available, as well as 10 repeat CT scans (during treatment), were analyzed. The rectal volume in the repeat CT scans appeared to be smaller than on the planning CT scan (average 74 cm³ and 84 cm³, respectively) causing on average systematic displacement (rotation) of the prostate during treatment. These data showed that a rectal volume of ≥ 90 cm³ on the planning CT scan was associated with a rotation of at least 2 degrees around the left-right axis (up to 6 degrees for a volume of 140 cm³). The position of the prostate in the repeat CT scans showed that a rotation of the prostate, caused by a smaller rectum, was associated with a rotation of the (base of the) seminal vesicles (SVs) out of the planning target volume for several patients.

A smaller rectal volume during treatment, with regard to the situation of the planning CT, can be explained by the development of loose or watery stools during RT for a large group of prostate cancer patients. Published data on diarrhea during RT are limited; toxicity is mostly reported in terms of overall toxicity scores and/or increased stool frequency, proctitis, and bleeding and not in terms of diarrhea. The prevalence of diarrhea during RT for prostate cancer was reported by De Meerleer et al. [6] to be 31% (prescribed dose of 72 Gy-78 Gy, 2 Gy/fraction). A much higher frequency was however reported by Fransson et al. [7]: an incidence in the range of 55-65% of loose or watery stools at week 5 of treatment (64 Gy-76 Gy, 2 Gy/fraction). In another study, Tsai et al [8] reported that hardly any increase in the incidence of diarrhea was seen during treatment (67 Gy, 1.8 Gy/fraction). The large variation in reported frequencies can probably be explained by differences in prescribed dose, treatment schemes (elective fields, margins), used definition of diarrhea, as well as likely differences in data collection (e.g. with or without questionnaires, prospective or retrospective studies).

In the present study, we investigated the hypothesis that because of a relatively large volume of the rectum visible on the planning CT scan, a clinically relevant systematic shift occurs in the position of the tumor during
RT for a subgroup of patients. In such cases, tumor control could be affected when the applied margins are not sufficient to compensate for this effect. We analyzed the dose-response data from the Dutch multi-center randomized phase III trial comparing 68 Gy with 78 Gy [9] to investigate this possible loss in tumor control.

Patients and methods

Patient group
We analyzed data from the Dutch Phase III trial randomizing between 68 Gy and 78 Gy. The main inclusion criteria were localized prostate cancer T1b-T4N0M0, no prior malignancies and no previous radiotherapy of the pelvis. Patient recruitment took place between June 1997 and February 2003. We selected patients entered in the study at the Erasmus Medical Center Erasmus Medical Center - Daniel den Hoed Cancer Center (EMC) in Rotterdam or The Netherlands Cancer Institute - Antoni van Leeuwenhoek Hospital (NKI/AvL) in Amsterdam (n = 575). We did not select patients from the other 2 participating hospitals, because their patients had not answered the checklists (with information on acute diarrhea) during treatment. For 7 patients of the selected group, no dose data were available, and for another group of 19 patients no acute toxicity data on diarrhea during RT was available. Therefore data of 549 patients could were analyzed in this study. Additional details of the total study population have been described elsewhere. [10]

Treatment
For all patients a planning CT scan was obtained before treatment. Before the planning CT scan (and during the treatment period), patients were asked to empty their bladder and drink half a liter of water, 1 h in advance. The Netherlands Cancer Institute – Antoni van Leeuwenhoek Hospital had a policy of rescanning patients with a very large rectum (≥ 150 cm³), and the Erasmus Medical Center had a policy to give mild laxatives before scanning. The dose prescription was according to the recommendations of the International Commission on Radiation Units and Measurements, with 2 Gy/fraction. [11]

The Gross Tumor Volume (GTV) was delineated on the planning CT scan as the prostatic capsule including the base of the seminal vesicles (SV) in cases in which only the prostate was the target and including the prostatic capsule with and without the SV (GTV1 and GTV2) in cases in which the SV were also the target. The Clinical Target Volume (CTV) was defined as the
delineated GTV. The anorectum was delineated on the CT scan from the anal verge until the inferior border of the sacro-iliac joints or to the point where the rectum was no longer close to the sacrum. For treatment planning a 1-cm margin from CTV to the Planning Target Volume (PTV) was applied for the first 68 Gy, with a margin of 5 mm (0 mm towards the rectum) for the 10 Gy boost, when applicable. The dose to the SV was prescribed within four treatment groups, based on the estimated risk of SV involvement using the Partin tables [12]: Group I, with an estimated risk < 10 %, 0 Gy; Group 2, with an estimated risk of 10 %-25 %, 50 Gy. Both groups containing T1b-T2a tumors only, with relatively low Gleason score and/or PSA levels). Group III, with an estimated risk > 25 % (including all T2b, T3a tumors and T1b-T2a with relatively high PSA level and/or Gleason score), 68 Gy; Group IV, the total dose of 68 Gy or 78 Gy (T3b-T4 only). The exact definition of the treatment groups is summarized in Table 1. During treatment the patient setup was verified using electronic portal imaging and an offline verification protocol, keeping systematic setup errors within 5 mm. Other details about treatment planning have been described previously. [10]

Table 1. Defined treatment groups (I, II, III and IV).

<table>
<thead>
<tr>
<th>Gleason score</th>
<th>iPSA (µg/l)</th>
<th>0-4</th>
<th>4-10</th>
<th>10-20</th>
<th>20-60</th>
<th>0-60</th>
</tr>
</thead>
<tbody>
<tr>
<td>Differentiation</td>
<td>T1b, T1c, T2a*</td>
<td>T2b*</td>
<td>T3a</td>
<td>T3b</td>
<td>T4</td>
<td></td>
</tr>
<tr>
<td>2-4 Good</td>
<td>I</td>
<td>I</td>
<td>I</td>
<td>II</td>
<td>III</td>
<td>IV</td>
</tr>
<tr>
<td>5-7 Moderate</td>
<td>I</td>
<td>II</td>
<td>II</td>
<td>III</td>
<td>III</td>
<td>IV</td>
</tr>
<tr>
<td>8-10 Poor</td>
<td>II</td>
<td>III</td>
<td>III</td>
<td>III</td>
<td>III</td>
<td>IV</td>
</tr>
</tbody>
</table>

Abbreviation: iPSA, initial prostate-specific antigen.
*According to American Joint Committee on Cancer 1997 guidelines.

**Definition of risk factors for geometric miss**

We defined a possible risk factor (RF1) for a geometric miss based on a rectum volume in the planning CT scan of ≥ 90 cm³ combined with the presence of diarrhea during RT. We hypothesized that diarrhea could cause a smaller volume of the rectum leading to a possible clinically relevant shift of rectum and prostate. Diarrhea was scored on a patient self-report questionnaire (grade 1-3) on a weekly basis: loose stools, loose to watery stools, watery stools. Patients had to report diarrhea (grade 1, 2 or 3) for at least 25 % of the treatment time to score for ‘diarrhea during treatment’. We calculated this percentage by dividing the number of times diarrhea was reported by the number of completed questionnaires. Apart from RF1, we
also evaluated the predictive value of volume ≥ 90 cm$^3$ on the planning CT scan and the presence of diarrhea > 25 % (yes/no) separately.

On the basis of the findings of de Crevoisier et al., [4] we defined the mean cross-sectional area (CSA) of the delineated anorectum as a second risk factor (RF2). RF2 was calculated by dividing the total volume of the delineated anorectum (including filling) by the length (difference in coordinates in anterior-posterior direction) of the delineated anorectum in centimeters. The predictive value of the mean CSA was tested at a cutoff of the median value and at a cutoff value of the upper quartile (RF2).

**Subgroups for analysis**

Because the dose to the SVs was different within the treatment groups (as described above), leading to different dose distributions, a potential difference existed in the risk of geometric miss. Therefore, we divided the patient population into three groups for the analysis: treatment group I (0 Gy to the SV), treatment group II (50 Gy to the SV) and treatment group III/IV (68/78 Gy to the SV). We chose to analyze treatment groups III and IV together, because the dose to the prostate and SV was similar; for all patients in the 68 Gy arm the dose to the SV was 68 Gy, for patients in the 78 Gy arm, the prescribed dose to the SV was 68 Gy in treatment group III and 78 Gy in treatment group IV.

**Statistical analysis**

We tested the predictive value of the defined risk factors RF1 and RF2, as well as the predictive value of a number of variables separately, using a multivariable Cox regression model (adjusted for hospital and dose group). Adjustment for hospital was done to adjust for the different levels of failures in the hospitals.

For the endpoint ‘Freedom From any biochemical or clinical Failure’ (FFF) we calculated biochemical failures according the ASTRO guidelines (American Society for Therapeutic Radiology and Oncology) of 3 consecutive rises. [13] However, we did use no backdating to the midpoint between last nonrising value and first rise, because of concerns of the stability in the failure rate when backdating is applied, as we have previously reported. [9] Clinical failures were defined as locoregional failure, distant metastasis or start of salvage hormonal therapy. The ‘dose group’ that was included in the multivariable testing referred to the ‘true’ dose that the patient had received during treatment: < 73 Gy (mean dose in this group of 67.9 Gy) or ≥ 73 Gy (mean dose of 77.9 Gy). All results with a $p$ value of 0.01 or below were considered as statistically significant; because of the ‘multiple testing’ in this study we did not choose a cutoff of 0.05 for statistical
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significance. We used ©SPSS for Windows software for the analyses, release 10.0 (SPSS, Chicago, IL).

Results

General statistics
In Table 2, the general statistics are summarized. The median follow-up time was 51 months. The mean age was 69 years (6.4 years, 1 SD). Treatment group I contained 18 % of the patient population (n = 99), group II 18 % (n = 101) and group III/IV 64 % (n = 349; 258 in group III, 91 in group IV). The mean volume of the delineated anorectum (including filling) was 82.7 cm³ and the mean anorectal length (cranio-caudal distance between most upper and lower delineated slide) was 11.9 cm. The mean horizontal cross sectional area (CSA) was 7.0 cm² and the median value was 6.6 cm². The CSA and the anorectum volume were highly correlated variables with a Pearson correlation coefficient of 0.92 (p < 0.001). With regard to the prevalence of diarrhea, 15 % reported loose or watery stools at baseline and 80 % reported at least once loose or watery stools during radiotherapy of whom 71 % reported diarrhea ≥ 25 % of the treatment time (67 % in group I, 75 % in group II, 71 % in group III/IV). The remaining 9 % of the patients, who reported diarrhea < 25 % of the time, all reported loose stools once (no watery stools).

Overall results for freedom from failure
The Freedom From Failure (FFF) for the total group was 56 % at 5 years (3 %, 1SE). The FFF in the low dose (67.9 Gy) and high dose group (77.9 Gy) was 49 % (4 %, 1SE) and 65 % (4 % 1SE), respectively. Within the treatment groups, the FFF at 5 years was 82 % in group I (5 %, 1SE), 62 % in group II (6 % 1SE) and 47 % in group III/IV (3 %, 1SE).

Predictive value of diarrhea plus large anorectum on CT scan (RF1)
Out of the 549 patients, 184 (34 %) had an anorectum volume including filling ≥ 90 cm³ (29 % in treatment group I, 39 % in group II, 29 % in group III/IV) of whom 141 (26 % of total population) reported diarrhea ≥ 25 % of treatment time. The number of patients fulfilling the criterion of RF1 was 18 %, 36 % and 25 % in treatment groups I, II and III/IV, respectively.
Table 2. Characteristics of the study population.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total group (n = 549)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
</tr>
<tr>
<td>Tumor stage</td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>100</td>
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<tr>
<td>T2</td>
<td>237</td>
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<tr>
<td>T3</td>
<td>205</td>
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<tr>
<td>T4</td>
<td>7</td>
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<tr>
<td>Treatment group</td>
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</tr>
<tr>
<td>I</td>
<td>99</td>
</tr>
<tr>
<td>II</td>
<td>101</td>
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<tr>
<td>III</td>
<td>258</td>
</tr>
<tr>
<td>IV</td>
<td>91</td>
</tr>
<tr>
<td>Randomization arm and actually given dose</td>
<td></td>
</tr>
<tr>
<td>68 Gy arm</td>
<td>274</td>
</tr>
<tr>
<td>- 68 Gy</td>
<td>274</td>
</tr>
<tr>
<td>78 Gy arm</td>
<td>275</td>
</tr>
<tr>
<td>- 78 Gy</td>
<td>248</td>
</tr>
<tr>
<td>- 74-76 Gy</td>
<td>9</td>
</tr>
<tr>
<td>- 68-72 Gy</td>
<td>18</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Rectum*</th>
<th>Mean values (SD):</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delineated volume including filling (cm³)</td>
<td>82.7 (26.7)</td>
</tr>
<tr>
<td>Delineated craniocaudal length# (cm)</td>
<td>11.9 (1.4)</td>
</tr>
<tr>
<td>Cross-sectional area (cm²)</td>
<td>7.0 (2.0)</td>
</tr>
</tbody>
</table>

* calculations include the total delineated anorectal tract
# absolute craniocaudal distance between most upper and lower delineated slide

The anorectum volume (including filling) had no predictive value as a continuous factor (results not shown) or at a cutoff of the median value, which was 78 cm³. It did have a significant predictive value at a cutoff of 90 cm³ for patients treated in treatment group III/IV (p = 0.01, Table 3) and no predictive value in treatment group I and II (p = 0.6 and 0.9, respectively). Diarrhea alone had no predictive value. However, RF1 (both diarrhea during treatment and an anorectum of at least 90 cm³ on the planning CT scan) was a highly significant predictor for FFF in treatment group III/IV (p = 0.001) whereas it was not for treatment groups I and II (p = 0.07 and 0.7, respectively, Table 3). These results are illustrated in Fig. 1: the Kaplan-Meier curves show the FFF for patient groups with and without RF1 for treatment group III/IV, stratified for the dose group (67.9 Gy and 77.9 Gy). The corresponding p value of the Log Rank test (adjusted for dose group) was 0.0002. The curves show a difference in FFF at 5 years of 30 % in the 67.9 Gy dose group: from 49 % (5 %, 1SE) for patients not at risk to 19 % (7 %, 1SE) for patients at risk. For the 77.9 Gy dose group a difference in FFF of 18 % is found at 5 years of follow up: from 59 % (6 %, 1SE) to 41 % (8 %, 1SE).
Table 3. Results of Cox regression analysis for the endpoint freedom from biochemical and clinical failure (FFF), per treatment group. Every variable is tested in a model adjusted for hospital and dose group. HR stands for hazard ratio. Significant results ($p \leq 0.01$) are in italics.

<table>
<thead>
<tr>
<th>Variable</th>
<th>I (n=99)</th>
<th>II (n=101)</th>
<th>III/IV (n=349)</th>
</tr>
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<tbody>
<tr>
<td>Anorectal volume</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\geq$median (78 cm$^3$)</td>
<td>1.7 0.6-4.5 (0.3)</td>
<td>0.8 0.4-1.7 (0.6)</td>
<td><strong>1.2 0.9-1.6 (0.3)</strong></td>
</tr>
<tr>
<td>$\geq$90 cm$^3$</td>
<td><strong>1.3 0.5-3.6 (0.6)</strong></td>
<td><strong>0.9 0.4-2.0 (0.9)</strong></td>
<td><strong>1.5 1.1-2.1 (0.01)</strong></td>
</tr>
<tr>
<td>Diarrhea $\geq$ 25 % RT</td>
<td><strong>9.0 1.2-70 (0.04)</strong></td>
<td><strong>1.0 0.4-2.6 (0.9)</strong></td>
<td><strong>1.2 0.9-1.8 (0.2)</strong></td>
</tr>
<tr>
<td>Anorectal vol $\geq$90 cm$^3$ and diarrhea $\geq$ 25 % RT*</td>
<td><strong>2.7 0.9-7.8 (0.07)</strong></td>
<td><strong>0.9 0.4-1.9 (0.7)</strong></td>
<td><strong>1.8 1.3-2.4 (0.001)</strong></td>
</tr>
<tr>
<td>CSA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\geq$ median (6.6 cm$^2$)</td>
<td><strong>2.7 0.9-7.6 (0.07)</strong></td>
<td><strong>1.0 0.5-2.2 (1.0)</strong></td>
<td><strong>1.1 0.8-1.5 (0.6)</strong></td>
</tr>
<tr>
<td>$\geq$8 cm$^2$#</td>
<td><strong>1.3 0.5-3.9 (0.6)</strong></td>
<td><strong>0.5 0.2-1.3 (0.1)</strong></td>
<td><strong>1.5 1.1-2.2 (0.02)</strong></td>
</tr>
</tbody>
</table>

Abbreviations: CSA = cross sectional area; F = risk factor; HR = hazard ratio; CI = confidence interval
*defined as risk factor 1 (RF1)  #defined as risk factor 2 (RF2)

Predictive value of cross-sectional area
The median cutoff value of the CSA (6.6 cm$^2$) had no predictive value for the FFF (Table 3). A cutoff at the quartile of 75 % (8.0 cm$^2$), defined as risk factor 2 (RF2), was associated with a decreased FFF in treatment group III/IV (hazard ratio of 1.5). This result was however (borderline) not significant ($p = 0.02$). For treatment group I and II, the hazard ratio’s at a cutoff of 8.0 cm$^2$ were 1.3 ($p = 0.6$) and 0.5 ($p = 0.1$), respectively. From the 25 % ($n = 135$) with RF2, 96 % had an anorectum volume including filling $\geq 90$ cm$^3$ and 73 % fulfilled the criterion for RF1.

Clinical failures for subgroups with significantly decreased FFF
For the patients in treatment group III/IV, we evaluated also the impact of RF1 and RF2 on the clinical failures only (FFCF). Adjusted for hospital and dose group, the HR of RF1 was 1.7 (95 % confidence interval 1.1-2.5, $p = 0.01$). For RF2 the hazard ratio (HR) was also 1.7 (95 % confidence interval 1.1-2.6, $p = 0.01$). The Kaplan Meier curves for the ‘risk -‘ and ‘risk+’ group ($n = 262$ and $n = 87$, respectively) are shown for RF1 in Fig. 2 for each dose group. The $p$ value of the corresponding Log Rank statistic (adjusted for dose group) was 0.009. The drop in FFCF at 5 years is similar for both dose groups (about 15 %): from 69 % (5 % 1SE) to 55 % (9 % 1SE) for the 67.8 Gy dose group and from 71 % (5 % 1SE) to 55 % (8 % 1SE) in the 77.9 Gy dose group.
Fig. 1 and Fig. 2. Kaplan-Meier curves of ‘freedom from biochemical or clinical failure’ (Fig. 1) and freedom from clinical failure’ (Fig. 2), for patients with and without risk factor 1 (anorectal volume ≥ 90 cm³ and diarrhea ≥ 25 % of the treatment time) for the subgroup ‘treatment group III/IV’. Curves are shown for the dose group 67.9 Gy and 77.9 Gy. The corresponding p value of the Log Rank test (adjusted for dose group) is 0.0002 (Fig. 1) and 0.0009 (Fig. 2), respectively.
Discussion

We found evidence in our trial data that tumor control was significantly decreased in patients for whom the patient model for treatment planning was suspected to be not representative for the patient anatomy during the actual treatment, owing to the large rectum visible on the planning CT scan.

This evidence was found for a subgroup of patients with an estimated SV involvement of ≥ 25 % (treatment group III/IV; that is, patients with T stage T2B-T4 and/or a combination of the risk factors PSA level of 20 μg/L - Gleason 5 or higher, PSA level > 4 - Gleason ≥ 8). For these patients, RF1 (anorectal volume ≥ 90 cm³ and at least 25 % of the treatment time diarrhea) was significantly associated with a decrease in tumor control (for FFF, as well as FFCF). In contrast, the RF2 (CSA ≥ 8 cm²) was only close to significance. Because the variable CSA and anorectal volume correlated highly, the RF2 would probably also become significant when diarrhea would become a part of the definition, as in RF1.

For patients (group I and II) with an estimated risk of SV involvement < 25 %, who were treated with a dose of 0-50 Gy to the SV, we found no significant decrease in FFF resulting from one of the two risk factors, although some HRs were quite large (e.g. a HR of 2.7 for RF1 in treatment group I). This patient subgroup was, however, much smaller and therefore the statistical power to identify a risk was limited. Therefore, we could not conclude whether the estimated large HR resulted from chance, or that there a significant effect would have been noted in a larger study population or after more follow-up data. In particular, the HR of 9.0 in treatment group I for the risk factor of diarrhea > 25 % of treatment time would be an interesting factor to investigate again when we have more events, because the present analysis is based on only 17 events of FFF in the total subgroup of 99 patients.

The findings of our study support the observations of De Crevoisier et al. [4] who described a significant decrease in tumor control (freedom from biochemical or clinical failure, according the ASTRO definition) for patients treated to 78 Gy, with a CSA on the planning CT scan above the median value of 11.2 cm². They found a decrease of more than 25 % in tumor control (FFF) 6 years after RT for 50 % of their patients (with a CSA greater than the median value). In our study we found a reduction of 20 % in FFF for the 77.9 Gy dose group at 5 years for a much smaller group at risk: about 25 % of treatment group III/IV, which is about 16 % of the total population. This could be explained by a number of differences between the two studies: our median CSA was 6.6 cm² but was much larger (11.2 cm²) for their population. Furthermore, we used a setup verification protocol to keep
systematic errors within a few mm while their patients had verification by films on a weekly basis. Another issue was that the margin for the first 68 Gy was 10 mm in our study. In contrast, the study by De Crevoisier et al. used a minimum of 7.5 - 10 mm from the CTV to the block edge in the posterior direction for the boost > 46 Gy, leading to an effective margin at the dorsal site of the prostate < 5 mm because of the beam penumbra.

The potential danger of a planning CT scan not being representative for the situation during treatment can probably be prevented by relatively simple to more complex procedures (different types of image guided radiotherapy) without increasing the margins. Currently, we use a new protocol in our clinic, including a dietary regimen and mild laxatives prior to the planning CT scan and during treatment (for patients with diarrhea, no laxatives are given). Although the policy of mild laxatives in the Erasmus Medical Center did not lead to the prevention of geometric miss in our trial, a more strict protocol, including diet, should solve most of the problems. For a subgroup of our patient population, we also have implemented a more complex solution by means of adaptive RT). Patients treated within the adaptive RT protocol undergo repeat planning after the first week of treatment to determine their mean prostate position and their mean rectum position, which have been established with cone-beam CT scanning during the first five fractions. In this protocol, the margins are reduced in the additional adaptive RT plan for the remaining treatment period, keeping the tumor coverage probability at least at the same level. Other groups have reported using a protocol with on-line matching on prostate markers, a straightforward method to avoid a geometric miss.

However, even with a dietary and laxative protocol, it can not be excluded that in a small number of patients a margin of 10 mm is not sufficient to take into account sub-clinical disease, errors in setup and delineation and relatively large organ motions owing to, for instance, severe diarrhea. The applied margin of 10 mm is currently considered as rather large when using prostate localization techniques such as cone beam CT, ultrasound or fiducial markers.

The greatest risk of a geometric miss is very likely to be at the site of the rectum and/or SV. First, for 70 - 80 % of prostate cancers the peripheral zone is involved, which is located at the dorsal (rectal) site of the prostate. [14,15] This site is also the place where we want tight margins and steep dose gradients to avoid toxicity of the rectum. However, when extracapsular disease is present, the dorsal site (adjacent to the anterior rectal wall) is the place where extensions are often found. [2] In particular, for patients at high risk for SV invasion and extracapsular extension, the true CTV could be very
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close to the delineated PTV at the dorsal site, leaving only a small margin to account for setup errors and organ motion.

Teh et al. [2] reported on extracapsular extension of prostate cancer and the radial distance. They concluded that attention for the coverage of sub-clinical disease is important, especially when the isodose lines become tight. They found an overall percentage of 26% of extracapsular disease in their study population of 712 patients up to 5 mm extensions and beyond and a median radial extension of 2 mm. They concluded that coverage of sub-clinical disease must be addressed first before addressing other issues, such as intensity-modulated RT and dose escalation, to avoid geometric miss.

Tinger et al. [16] concluded that margins of 9.6 mm in the anterior-posterior direction are needed to cover 95% of the uncertainty in setup and organ motion when the SV are involved (and 8 mm in case they are not involved). Rasch et al. [3] calculated that the margin from CTV to PTV to take into account the errors caused by organ motion, patient setup, and target delineation, should be at least 9.5 mm in the AP direction for a coverage of 95% of the treatment sessions for prostate cancer. This suggests that the 10 mm that we used in our study (only 0.5 mm extra) in the anterior-posterior direction was not sufficient to cover for extra risks for some patients who had for instance extracapsular extension, full planning CT scans and/or severe diarrhea during treatment. Also, the margin of 0 mm towards the rectum for the boost of 10 Gy is probably not an optimal protocol for dose escalation.

The magnitude of loss in tumor control probability (TCP) we found in this study is larger than previously estimated by our group [17,18]. Van Herk et al. [17] calculated that with a systematic error of 3.6 mm and a random error of 3.3 mm, a TCP loss due to these errors of 1% is expected when a CTV-PTV margin of 10 mm is applied (with a typical dose distribution of a three-field technique similar to the treatment in our trial). Within treatment group III/IV, we have had a TCP loss in the range of 15% - 25% for about a quarter of the population, which is about 4% - 5% for the total group of 349 patients. This could have been partly caused by extracapsular extensions, which makes the assumption that the GTV (the prostate) is assumed to be the CTV invalid. Furthermore, in these calculations, it was assumed that no overall systematic shift occurred between the position of the prostate on the planning CT scan and during treatment. We know now that this is not the case for the patients with a large rectum on the planning CT scan. We will perform additional simulations in the near future to study the observed TCP losses in relation to these issues.
Conclusions

Tumor control was significantly decreased in a subgroup of patients with a large rectum filling visible in the planning CT scan who were treated with conformal techniques and a 10 mm margin and who had an estimated risk of SV involvement of > 25 %. Current image protocols offer several solutions to further optimize the treatment. Additional research is needed to evaluate whether these localization techniques can prevent geometric misses.
References


